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TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED OFFICE (DO/US)

PCT/SE99/02315	10 DECEMBER 1999	14 DECEMBER 1998
International Application Number	International Filing Date	Priority Date(s) Claimed

NEW PHARMACEUTICAL FORMULATION
Title of Invention

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Applicant(s) for DO/US

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Date of Deposit February 1, 2000.
I hereby certify that this paper is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1 10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D C 20231

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To the United States Designated Office (DO/US):

I. Accompanying this transmittal letter are certain items which are required under 35 U.S.C. 371 in order that United States National processing of the above identified International application may commence:

(X) at the expiration of the applicable time limit under PCT Articles 22 and 39(1) according to the provisions of 35 U.S.C. 371(b).

( ) as soon as possible upon receipt of this express request under 35 U.S.C. 371(f).

1. The U.S. National fee [35 U.S.C. 371(c)(1)]

a. ( ) was previously transmitted by applicant on (date)____.

b. (**X**) is submitted herewith as follows:

FOR	NO. FILED	NO. EXTRA	SMALL ENTITY RATE	FEE	or	OTHER THAN SMALL ENTITY RATE	FEE
Basic Fee	(USPTO NOT ISA OR IPEA)		////	$485	or	/////	**$970**
Total Claims	-20 =	--	x 9 =		or	x18 =	**$**
Ind. Claims	**6 - 3**	3	x 39 =		or	x78 =	**$234**
(**X**) Multiple Dependent Claim Presented			+130 =		or	+260 =	**$260**
	TOTAL NATIONAL FEE		$____		or		**$1464**

i. (**X**) A check in the amount of **$1464** is enclosed.

ii. ( ) Please charge the filing fee, multiple dependent claim fee (if applicable), excess independent claims fee (if applicable), and excess total claims fee (if applicable) **to Deposit Account No. 23-1703**.

iii. (**X**) The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to **Deposit Account No. 23-1703**. A duplicate copy of this sheet is enclosed.

(iv) ( ) The filing fee is not enclosed.

2. A copy of the International application as filed [35 U.S.C. 371(c)(2)]:

a. (**X**) is transmitted herewith.

b. ( ) is not required as the application was filed with the United States Receiving Office.

c. ( ) has been transmitted

i. ( ) by the International Bureau. Date of mailing of the application (from form PCT/IB/308): _____ A copy of form PCT/IB/308 is enclosed.

ii. ( ) by applicant on (date) _____.

3. A translation of the International application into the English language [35 U.S.C. 371(c)(2)]:

a. ( ) is transmitted herewith.

b. (**X**) is not required as the application was filed in English.

c. ( ) was previously transmitted by applicant on (date)_____.

4. Amendments to the claims of the International application under PCT Article 19 [35 U.S.C. 371(c)(3)]:

a. ( ) are transmitted herewith.

b. ( ) have been transmitted

i. ( ) by the International Bureau. Date of mailing of the amendments (from form PCT/IB/308): _____.

ii. ( ) by applicant on (date) _____.

c. (**X**) have not been transmitted as

i. ( ) no notification has been received that the International Searching Authority has received the Search Copy.

ii. ( ) the Search Copy was received by the International Searching Authority but the Search Report has not yet issued. Date of receipt of Search Copy (from form PCT/ISA/202): _____.

iii. ( ) applicant chose not to make amendments under PCT Article 19. Date of mailing of Search Report (from form PCT/ISA/210):

iv. (X) the time limit for the submission of amendments has not yet expired. The amendments or a statement that amendments have not been made will be transmitted before the expiration of the time limit under PCT Rule 46.1.

5. A Translation of the amendments to the claims under PCT Article 19 [35 U.S.C. 371(c)(3)]:

a. ( ) is transmitted herewith.

b. ( ) is not required as the amendments were made in the English language.

c. (X) has not been transmitted for reasons indicated at point I.4.b. or c. above.

6. Two executed declarations for patent application of the inventor [35 U.S.C. 371(c)(4)] complying with 35 U.S.C. 115:

a. ( ) was previously submitted by applicant on (date) _____

b. **(X)** are submitted herewith; and such oaths or declarations

i. **(X)** are attached to the application.

ii. **(X)** identify the application and any amendments under PCT Article 19 which were transmitted as stated in points 1.2.b. or c. and 1.4. and states that they were reviewed by the inventor as required by 37 CFR 1.70.

c. ( ) will be submitted subsequently.

II. Concerning other documents:

1. An International Search Report or Declaration under PCT Article 17(2)(a):

a. ( ) has been transmitted by the International Bureau. Date of mailing (from form PCT/IB/308): _____ A copy of form PCT/IB/308 is enclosed

b. ( ) is not required as the application was searched by the United States International Searching Authority.

c. ( ) A copy of the International Search Report is transmitted herewith.

d. ( ) has been submitted by applicant on (date) _____.

2. A Statement of prior art under 37 CFR 1.97 and 1.98:

a. **(X)** is transmitted herewith including copies of the references cited on the attached form PTO-1449. Also enclosed is a copy of the International-Type Search Report issued in the Swedish priority application.

b. ( ) will be transmitted within THREE MONTHS of the date of submission of requirements under 35 U.S.C. 371(c).

c. ( ) was previously submitted by applicant on _____, in application serial no. _____.

3. **(X)** Two executed Assignments are transmitted herewith for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

a. ( ) Please charge the $40.00 assignment recordation fee to Deposit Account No. 23-1703.

b. **(X)** Enclosed is a check in the amount of **$40**.

4. **Other document(s) or information included:**
- Copy of PCT/RO/101 - The PCT Request Form; and
- a return postcard.

Respectfully submitted,

1 February 2000
DATE

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enclosures

NEW PHARMACEUTICAL FORMULATION

Field of the invention

This invention is related to new oral pharmaceutical dosage forms comprising a H^+, K^+-ATPase inhibitor, a gastric antisecretory prostaglandin analogue compound, and optionally an additional drug such as a calcium channel blocking agent, especially for use in the treatment and prophylaxis of gastrointestinal disorders. More specifically the invention is related to new dosage forms comprising omeprazole and misoprostol. The invention is also related to a combination of the three categories of drugs, i.e. the H^+, K^+-ATPase inhibitor, the gastric antisecretory prostaglandin analogue and the calcium channel blocking agent. Furthermore, the invention refers to a method for the manufacture of the described dosage forms and their use in medicine, as well as blisterpacks comprising these medicaments.

Background of the invention and prior art

H^+, K^+-ATPase inhibitors, such as the the proton pump inhibitors known under the generic names omeprazole, lansoprazole, pantoprazole, rabeprazole and leminoprazole are for instance described in EP 5129, EP 174 726, EP 166 287, GB 2 163 747 and WO 90/06925. The expression H^+, K^+-ATPase inhibitors and proton pump inhibitors are interchangable with each other within the context of the present application. Proton pump inhibitors are generally known to be useful for inhibiting gastric acid secretion in mammals and man by controlling gastric acid secretion in the final step of the secretory pathway. They heal gastric as well as duodenal ulcers in patients on continuous treatment with Non-steroidal anti-inflammatory drugs (NSAID) as in non-NSAID users. WO 96/01735 describes new fixed dosage forms comprising a proton pump inhibitor and an NSAID and their use in the treatment or prevention of gastrointestinal side-effects associated with NSAID treatment.

Prostaglandin analogue compounds, such as the ones known under the generic names misoprostol, enoprostil, enisoprost, rosaprostol and miraprostal are orally active PGE_1 -

analogues with mucosal protective and antisecretory properties, and these type of compounds are for instance described in US 3,965,143 and US 4,178,457. They are mainly used for prevention of gastric and duodenal ulcers associated with NSAID treatment. Usually they are administered in separate, single unit dosage form, and sometimes in combination with an NSAID in a fixed dosage form.

For gastric antisecretory prostaglandin analogues there are adverse drug reactions reported. The use of misoprostol for instance, may cause diarrhoea, abdominal pain and other adverse effects connected to the gastrointestinal system. Dosage regimen for misoprostol includes frequently intake of a dosage form, sometimes up to 4 times a day. This frequent intake, in addition to the undesired gastrointestinal side-effects with gastric antisecretory prostaglandin analogues implicates problems with compliance. On the other hand, the proton pump inhibitor, omeprazole, has only few dosage related adverse effects.

A combination of two or more active agents achieving similar physiological effect, but working through different mechanisms, usually gives a possibility to reduce the doses of each single drug and still achieve the desired effect. This will reduce the risk for dose dependent adverse side-effects. Furthermore, if one of the drugs fails due to individual patient response, the other component of the treatment regimen may be successful.

These factors implicates advantages of combining two or more antiulcerative drug in general, and to combine misoprostol with other antiulcerative drugs in particular. Administration of two or even more different dosage forms to the patient is not convenient or satisfactory for achieving the most optimal result. As patient compliance is a major factor in receiving a good medical result, it would be advantageous to combine the different drugs into one single pharmaceutical dosage unit, which reduces the number of pills for the patient at each dosing occasion. If one or more of the drugs can be provided in dosage forms with extended release the efficacy may be further enhanced.

Previously suggested combination therapies comprising antiulcerative agents are for instance combinations of a histamine H_2- receptor antagonist, such as cimetidine or ranitidine, and sucralfate. Other proposed therapies are for instance a combination of omeprazole and sucralfate, a combination of ranitidine and cimetidine, or a combination of ranitidine and misoprostol. See for instance Van Deventer GM et al., Am J Med 1985; 79: 39 - 44, and Houston LJ et al, Am J Gastroenterol 1993; 88: 675 - 679.

A combination therapy of misoprostol and a calcium channel blocking agent, such as verapamil, has been proposed and tested with respect to mucosal-protective effects in rats by reducing leukotriene synthesis and increasing prostaglandin synthesis. See Fedorak, R.N. et al, Gastroenterology 1992;102: 1229-35.

To combine the proton pump inhibitor omeprazole and the gastric antisecretory prostaglandin analogue enprostil for the treatment of gastrointestinal disorders is known from Tari, A. et al, Digestive Diseases and Sciences, 1997; 42: 1741-1746 and from Meijer, J.L. et al, Digestive Diseases and Sciences, 1994; 39: 609-616.

However, a fixed unit dosage form comprising a H^+, K^+-ATPase inhibitor in combination with a gastric antisecretory prostaglandin analogue has so far not been suggested.

Furthermore, there is no suggestion or description in the prior art of a combination comprising a H^+, K^+-ATPase inhibitor, a gastric antisecretory prostaglandin analogue and a calcium channel blocking agent. Neither is the Applicant aware of any oral pharmaceutical dosage forms comprising such a combination, especially not in the form of a blister pack or a fixed unit dosage form.

Summary of the invention

One aspect of the present invention is to provide a fixed unit dosage form for oral administration comprising a H^+, K^+-ATPase inhibitor and a gastric antisecretory prostaglandin analogue.

A further aspect of the invention is to provide dosage forms of a H^+, K^+-ATPase inhibitor and a gastric antisecretory prostaglandin analogue, wherein the latter is in a form which provides extended release, such a dosage form reduces dosing frequency and dose related adverse side-effects.

An additional aspect of the invention is to provide a combination therapy of a H^+, K^+-ATPase inhibitor, a gastric antisecretory prostaglandin analogue, and a component which potentiates the effect of the prostaglandin analogue, e.g. a calcium channel blocking agent. The combination may be provided in the form of fixed unit dosage forms.

Detailed description of the invention

According to the present invention, a fixed dosage form comprising a H^+, K^+-ATPase inhibitor, a gastric antisecretory prostaglandin analogue compound, and optionally a calcium channel blocking agent, may principally be constructed in the form of a two-layer tablet, or a tablet core layered with a coating layer, or a press-coated tablet, wherein the different drugs are situated in different parts of the tablet. Alternatively, the dosage form may be a tablet or a capsule comprising either two or three populations of units each one containing one of the drugs, or a population of multiple layered units comprising a combination of the different drugs, or they may be constructed as a capsule containing one or two of the drugs as a population of units and the other drug as a single unit also positioned within the same capsule.

Preferred types of dosage forms according to the invention are described more in detail below under separate headings, and in the following examples.

Two-layer tablet

One layer comprises the proton puimp inhibitor as a multitude of enteric coated pellets dispersed in pharmaceutically acceptable excipients. These pellets may have the characteristics of immediate release, delayed pulsed release, delayed dual pulsed release, delayed multiple pulsed release or extended release, or any combination thereof. If the proton pump inhibitor is to be constructed as an extended release part layer, it may be designed in the form of a hydrophilic matrix layer comprising the proton pump inhibitor. In this latter situation appropriate measures for protecting the proton pump inhibitor from contact with acidic fluids has to be taken.

The other layer comprises a gastric antisecretory prostaglandin analogue, and optionally a calcium channel blocking agent. This layer may be formulated to provide immediate or extended release of the drug(s). The extended release characteristics may be achieved by using membrane coated extended release pellets dispersed in pharmaceutically acceptable excipients or by dispersing the drug in a hydrophilic or hydrophobic matrix with extended release properties. Immediate release characteristics may be achieved by using a conventional tablet granulation procedure, or by incorporating the prostaglandin analogue in fast dissolving pellets, which are dispersed in pharmaceutically acceptable excipients. It is also possible in a first layer to include the proton pump inhibitor pellets together with the pellets comprising the prostaglandin analogue, and optionally in a second layer include a calcium channel blocking agent.

Tablet core comprising one drug layered with a second drug

Each tablet comprises a tablet core containing a proton pump inhibitor which tablet core is spray coated with a layer comprising a gastric antisecretory prostaglandin analogue. The tablet cores may be prepared as described below under the heading " *Press-coated/coated tablets*". The prepared tablets which are enteric coated are further layered with a suspension comprising the prostaglandin analogue. Alternatively, the tablet cores are layered in the same way as described below for pellets preparation. However, a prepared

tablet core has a larger size than cores intended for pellets preparation, i.e. preferably the tablet core has a size of 3 - 12 mm in diameter.

Press-coated/ coated tablets

An inner tablet core is prepared by tableting technique according to known art. The tablet core comprises one of the active ingredients, preferably a proton pump inhibitor, optionally in combination with a calcium channel blocking agent. This tablet core is then coated with an enteric coating layer, and optionally a separating layer has been applied before the enteric coating layer. The enteric coating layer protects the acidic susceptible proton pump inhibitor from gastric acid, i.e. it is a layer not dissolving in gastric acid environment but dissolving or disintegrating in the small intestines. A further coating layer comprising the second active ingredient, optionally in combination with a calcium channel blocking agent, is applied on the enteric coating layer by compression. Either the tablet core or the outer layer may give the characteristics of an extended or immediate release preparation.

Tablet or capsule comprising a multitude of drug-containing units

Such dosage forms my be divided into two principally different categories; e.g. (i) one-population of multiple layered units, and (ii) two-populations of units.

(i) One-population of multiple layered units intended for tablet or capsule formulations.

The first category comprising one population of equally constructed units or pellets, optionally dispersed in a pharmaceutically acceptable tablet excipient.

Each unit comprises a proton pump inhibitor and a gastric antisecretory prostaglandin analogue as the pharmaceutically active agents. The units contain multiple layers and the different active substances are situated in different layers. The proton pump layer is positioned on the inside of an enteric coating layer, optionally a separating layer may be positioned in between the proton pump layer and the enteric coating layer. The layer comprising a gastric antisecretory prostaglandin analogue, and optionally a calcium

channel blocking agent, is positioned exterior to the proton pump layer, but it may be positioned interior or exterior with regard to the enteric coating layer.

The proton pump inhibitor comprising layer may have characteristics of immediate release or extended release, which also is applicable for the layer comprising the gastric antisecretory prostaglandin analogue, though extended release is preferred. The prepared drug containing units may be filled in capsules or mixed with pharmaceutically acceptable tablet excipients and compressed to multiple unit tablets.

(ii) Two-populations of units intended for tablet or capsule formulations.
The second category comprises a mixture of two different populations of within each population equally constructed units or pellets, optionally dispersed in a pharmaceutically acceptable tablet excipients. One population comprises a proton pump inhibitor, and the other population comprises a gastric antisecretory prostaglandin analogue as the pharmaceutically active agent. Optionally, a third population of units comprising a calcium blocking agent is included in the mixture.

These formulations are based on the mixing of a population of units comprising a gastric antisecretory prostaglandin analogue with a population of units comprising a proton pump inhibitor. The mixture is filled in capsules, or further mixed with pharmaceutically acceptable tablet excipients and compressed to a tablet. The tablet excipients may be previously granulated or just admixed to the layered units before the compression to tablets.

Units comprising a gastric antisecretory prostaglandin analogue.
These units may be prepared by prilling, extrusion and spheronization, congealing, direct pelletization in a mixer, melt granulation with suitable polymeric additives, by incorporation in porous carriers, or by layering on a starting seed, or any other suitable techniques known in the art. The units may be formulated with immediate or extended

release characteristics. If suitable, an additional coating layer providing extended release may be applied onto the units.

To increase the residence time in the stomach for the units comprising a gastric antisecretory prostaglandin analogue, the gastric antisecretory prostaglandin analogue is included in a hydrophilic matrix together with a suitable concentration of a sodium hydrogen carbonate and formulated to pellets. When the pellets come in contact with the acidic gastric environment they develop small bubbles of carbon dioxide making the density of these pellets to decrease, and the pellets to flow in the stomach.

Units having immediate release characteristics may be prepared by incorporating the active substance in porous amorphous silica particles or by layering the active substance on sugar seeds.

Units comprising a proton pump inhibitor.
These units may be prepared for either immediate release, extended release or delayed pulsed release of the proton pump inhibitor. WO 97/ 02020 describes pellets of pantoprazole coated with extended release membrane which technology is suitable also for other extended release units. Units suitable for immediate release of the proton pump inhibitor are described in EP 502 556 and units especially designed for use in tableted dosage form are described in WO 96/ 01624, hereby incorporated by references.

Capsule comprising two or more drugs in a single unit in combination with multiple units.
The capsule comprises one drug in a single unit, i.e. a tablet, and one or two drugs in the form of two populations of units, or one population of units and one or two single tablets.

Units suitable for a capsule formulation may be prepared as described above, i.e. (i) one-population of multiple layered units comprising a proton pump inhibitor and a gastric antisecretory prostaglandin analogue, or (ii) two-populations of units. The capsule may

comprise two or three different drugs, i.e. a third population of units comprising a calcium channel blocking agent may be included.

The single unit may comprise any of the drugs, i.e. the proton pump inhibitor, the gastric antisecretory prostaglandin analogue, or optionally the calcium channel blocking agent. When the single unit comprises the prostaglandin analogue, it may have immediate or extended release characteristics. Immediate release single units are preferably constructed according to principles known in the art. Extended release single units are preferably constructed as hydrophilic matrix units, or as hydrophobic matrix units, or as membrane coated units.

Techniques for application of layers.

The layer can be applied by coating or layering procedures in suitable equipments such as a coating pan, a coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the coating process. As an alternative the layer(s) may be applied by using powder coating or press-coating techniques.

Excipients.

Different pharmaceutically acceptable excipients may be used in combination with the active substances in the claimed dosage forms. Such excipients are for instance binding agents, fillers, pH-buffering substances, pigments and the like.

Separating layer(s).

Suitable materials for the separating layer are pharmaceutically acceptable compounds such as, for instance, sugar, or filmforming compounds as polyethylene glycol, polyvinyl pyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methylcellulose, carboxymethylcellulose sodium and others, used alone or in mixtures. Additives such as plasticizers, colorants, pigments, fillers, anti-tacking and anti-static agents, such as for instance magnesium stearate, titanium dioxide, talc, pH-buffering substances and other additives may also be

included into the separating layer. The separating layer is composed in such a way that it has properties to be water soluble or disintegrating in water.

Enteric coating layer(s).

The enteric coating layer material may be dispersed or dissolved in water or dissolved in suitable organic solvents. As enteric coating layer polymers one or more, separately or dissolved in combination, of the following can be used, but are not restricted to; e.g. methacrylic acid copolymers, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethyl ethylcellulose, shellac or other suitable enteric coating layer polymer(s) known in the art.

Additives such as dispersants, colorants, pigments, additional polymers e.g. poly(ethylacrylat, methylmethacrylat), anti-tacking and anti-foaming agents may also be included into the separating layer and/or the enteric coating layer or in an additional tablet coat as described below. Other compounds may be added to increase film thickness and to decrease diffusion of acidic gastric juices into the acid susceptible core material. The enteric coating layer(s) constitutes a thickness of approximately at least 10 μm, preferably more than 20 μm. The maximum thickness of the applied enteric coating layer(s) is normally only limited by processing conditions.

The enteric coating layers may also contain pharmaceutically acceptable plasticizers to obtain desired mechanical properties. Such plasticizers are for instance, but not restricted to, triacetin, citric acid esters, phthalic acid esters, dibutyl sebacate, cetyl alcohol, polyethylene glycols, glycerol monoesters, polysorbates or other plasticizers and mixtures thereof. The amount of plasticizer is preferably optimized for each formula, in relation to the selected polymer(s), selected plasticizer(s) and the applied amount of said polymer(s).

Over-coating layer.

Pellets covered with enteric coating layer(s) may further be covered with one or more over-coating layer(s). The over-coating layer(s) can be applied to the enteric coating layered pellets by coating or layering procedures in suitable equipments such as coating pan,

coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the coating or layering process. The materials for over-coating layers are chosen among pharmaceutically acceptable compounds such as, for instance sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methyl cellulose, carboxymethylcellulose sodium and others, used alone or in mixtures. Additives such as plasticizers, colorants, pigments, fillers, anti-tacking and anti-static agents, such as for instance magnesium stearate, titanium dioxide, talc and other additives may also be included into the over-coating layer(s). The maximum thickness of the applied over-coating layer(s) is normally only limited by processing conditions.

Hydrophilic matrix.

The active substance, i.e. the drug, is embedded in a hydrophilic polymer optionally together with pharmaceutically acceptable excipients. Suitable hydrophilic polymers are for instance hydroxypropyl methylcellulose, hydroxypropyl cellulose, ethylhydroxy ethylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, sodium carboxymethyl cellulose, methyl cellulose, poloxamer, polyethylene oxides, polyvinylpyrrolidone, polyvinyl alcohols, tragacanth, xanthan and guar gums or any other suitable hydrophilic polymer(s). These polymers can be used alone or in mixtures with each other.

The amount of hydrophilic polymer in the matrix is preferably 15 - 85 % w/w (calculated on the unit weight) of a hydrophilic polymer(s) chosen among the above mentioned. Especially preferred polymers in the hydrophilic matrix unit are hydroxypropyl methylcellulose or polyethylene oxides.

Excipients preferred in the matrix are fillers which will result in technically good tableting properties, i. e. sodium aluminium silicate, mannitol or calcium phosphate (Emcompress™). A preferred matrix comprises 15 - 85 % w/w (calculated on the unit weight) of a hydrophilic polymer chosen as above, and 80 - 10 % w/w (calculated on the unit weight) of sodium aluminium silicate or calcium phosphate (Emcompress™).

Hydrophobic matrix.

The active substance, i.e. the drug, is embedded in a hydrophobic matrix optionally together with pharmaceutically acceptable excipients. The hydrophobic matrix comprises a hydrophobizing agent and/or a hydrophobic polymer. Suitable material for the hydrophobic matrix are for instance a hydrophobizing agents such as cetanol, cetostearyl alcohol, cetyl palmitate, waxes like carnauba wax, paraffin, magnesium stearate, sodium stearyl fumarate, and medium- or long- chain glycerol esters alone or in any mixtures. Hydrophobic polymers are exemplified by for instance polyvinyl chloride, ethyl cellulose, polyvinyl acetate and acrylic acid copolymers, such as Eudragith™ RS and RL. The polymers may be used alone or as mixtures. Furthermore, the polymers may be combined with the hydrophobizing agent.

As binders for the hydrophobic matrix may be used either hydrophilic or hydrophobic polymers.

It is important that the matrix comprises at least one component that is soluble in aqueous media such as the intestinal fluids. This component dissolves and leaves a porous network open for passage of dissolving fluids and dissolved drug. This soluble component may for instance be a sugar. It is preferred that the matrix comprises 10 - 70 % w/w (calculated on the unit weight) of a hydrophobizing agent or a hydrophobic polymer and 10-70% w/w of a water soluble component, both described above, or any combinations thereof.

Another preferred matrix comprises as an additive a slightly soluble or less soluble component. As such components may any of the following be added: sodium aluminium silicate, calcium phosphate, aerosil, titanium dioxide, magnesium carbonates, or other neutral or alkaline compounds that are slightly soluble or less soluble, herein with regard to solubility in water. Slightly soluble is defined in compliance with the European Pharmacopea (Edition 3) under the heading "General notices". Such a matrix comprises preferably 10 - 70 % w/w (calculated on the unit weight) of a hydrophobizing agent or a

hydrophobic polymer or any combinations thereof, together with preferably 10 - 70 % w/w of a slightly soluble or less soluble component. As such a component is especially preferred sodium aluminium silicate.

The final dissolution profile may sometimes be adjusted by thermal treatment of the hydrophobic matrix unit for a short period, to achieve temperatures at or above the softening temperature of the hydrophobizing agents.

Particles comprising oily material, such as for instance misoprostol.

One way of preparing a free-flowing particle of oily/greasy/sticky material is to incorporate it into inorganic porous particle material, such as for instance ceramic hydroxy apatite or amorphous silica. The ceramic hydroxy apatite has preferably a range particle diameter size between 5 - 250 μm, more preferably 80 - 150 μm, a nominal pore diameter between 50 - 1 000 Å, more preferably 500 - 1 000 Å; and a surface area between 40 - 50 m^2 /g. The amorphous silica has preferably a median pore diameter between 50 - 1 000 Å, more preferably 50 - 200 Å; a pore volume of 0.8 - 1.2 ml/g; and a surface area between 500 - 600 m^2/g.

The incorporation of the oily material may be accomplished by known conventional methods, such as dissolve the oil in a suitable solvent and then add the porous particle material and dry the mixture. Alternatively, the oil may be mixed directly with the porous particle material, or the incorporation may be done using phase separation from solution containing particles accomplished by the addition of a non-solvent. The loaded porous particles can be filled into capsules or compressed to tablets.

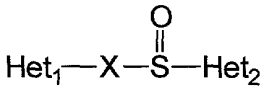
Preparation of particles comprising oily material in small amount may also be accomplished by conventional methods, such as layering or coating on inert seeds or by extrusion/ spheronization.

Tablet coat

Prepared tablets are optionally covered with film forming agent(s) to obtain a smooth surface of the tablet and further enhance the stability of the tablet during packaging and transport. Such a tablet coat comprising a polymeric material may further comprise additives like anti-tacking agents, colorants and pigments or other additives to obtain a tablet of good appearance. The tablet coat may especially comprise a pigment to protect light sensitive components of the dosage form.

Active ingredients.

I) H^+, K^+-ATPase inhibitors, i.e. proton pump inhibitors suitable for the claimed therapies and the pharmaceutical formulations according to the present invention are compounds of the general formula I, an alkaline salt thereof, one of the single enantiomers thereof or an alkaline salt of one of the enantiomers



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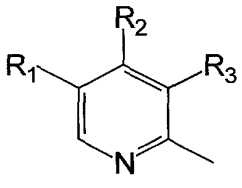

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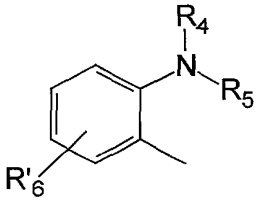

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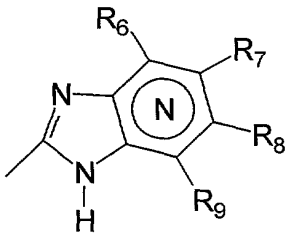

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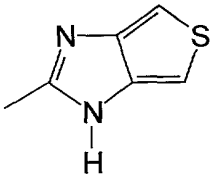

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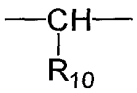

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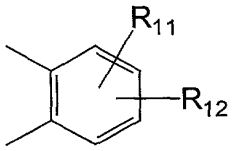


wherein

N in the benzimidazole moiety means that one of the ring carbon atoms substituted by R_6-R_9 optionally may be exchanged for a nitrogen atom without any substituents;

R_1, R_2 and R_3 are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

R_4 and R_5 are the same or different and selected from hydrogen, alkyl and arylalkyl;

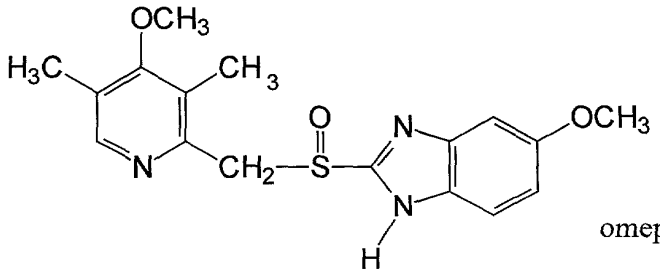
R_6' is hydrogen, halogen, trifluoromethyl, alkyl or alkoxy;

R_6-R_9 are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, haloalkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolinyl, trifluoroalkyl, or adjacent groups R_6-R_9 form ring structures which may be further substituted;

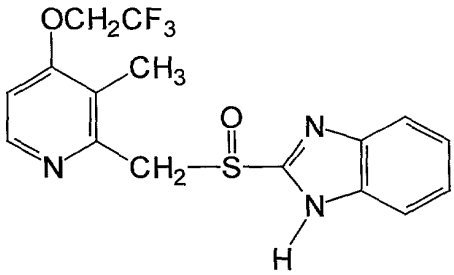
R_{10} is hydrogen or forms an alkylene chain together with R_3 and

R_{11} and R_{12} are the same or different and selected from hydrogen, halogen or alkyl.

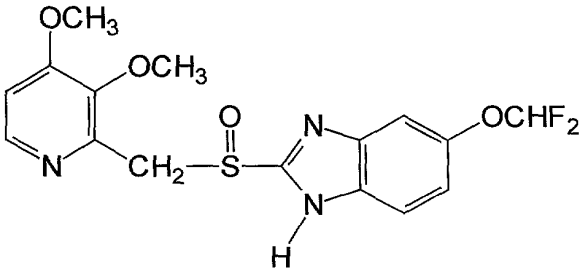
Examples of specifically interesting compounds according to formula I are



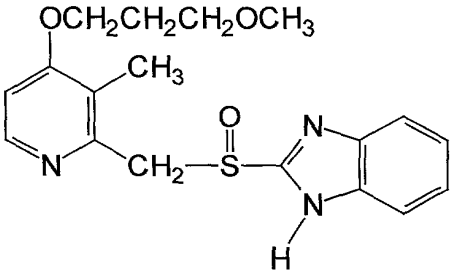
omeprazole



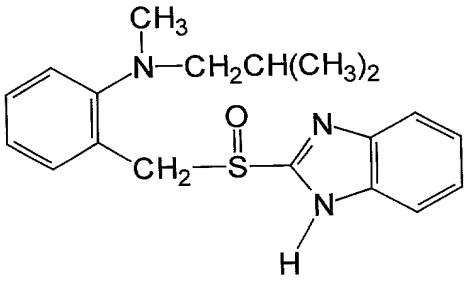
lansoprazole



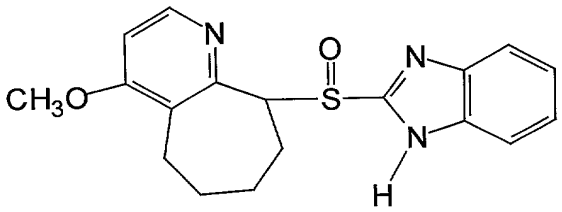
pantoprazole

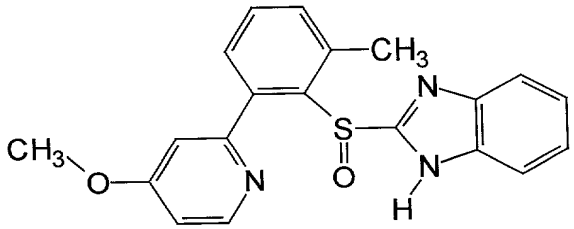


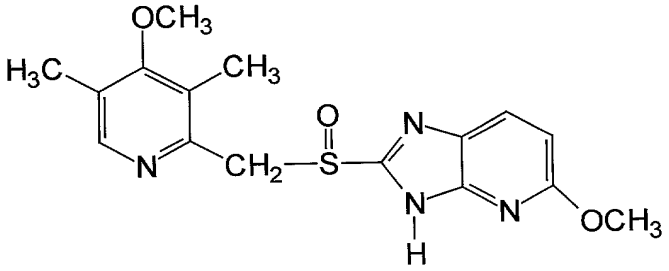
pariprazole

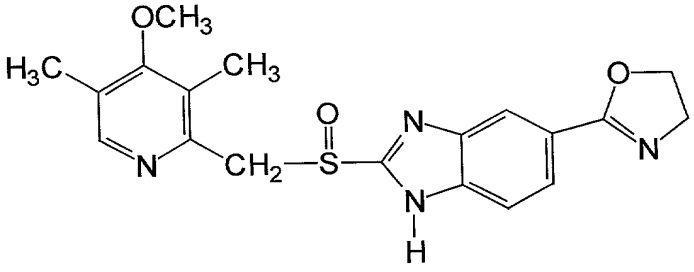


leminoprazole







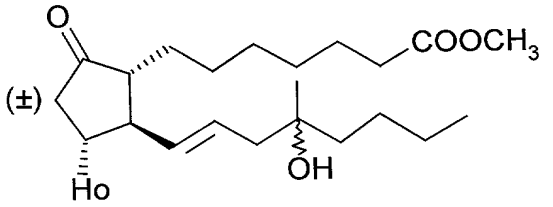


The compound suitable for the formulations according to the present invention may be used in neutral form or in the form of an alkaline salt, such as for instance the Mg^{2+}, Ca^{2+}, Na^{+} or K^{+} salts, preferably the Mg^{2+} salts. The compounds may also be used in the form of one of its single enantiomers or an alkaline salt of the single enantiomer.

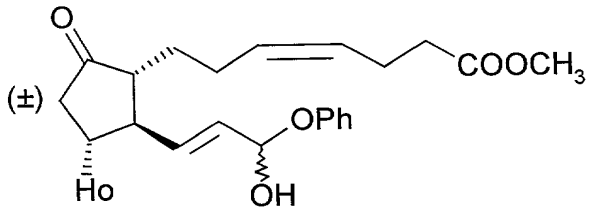
Preferred compounds for the oral pharmaceutical preparations according to the present invention are omeprazole, a magnesium salt of omeprazole or a magnesium salt of the (-)-enantiomer of omeprazole. Omeprazole and related substances as well as their preparations are described in EP 5129, EP 124 495, WO 95/01977, WO 94/27988 hereby incorporated in a whole by references.

The above compounds are susceptible to degradation/transformation in acidic and neutral media. Generally, the degradation is catalyzed by acidic reacting compounds and the active compounds are stabilized with alkaline reacting compounds. There are different enteric coating layered preparations comprising omeprazole as well as other proton pump inhibitors described in the prior art, see for instance US-A 4,853,230, WO 95/ 01783 and WO 96/ 01624. Especially, the latter describes alternative manufacturing methods for the preparation of enteric coating layered pellets comprising omeprazole and similar compounds. These patents are hereby incorporated in whole by references.

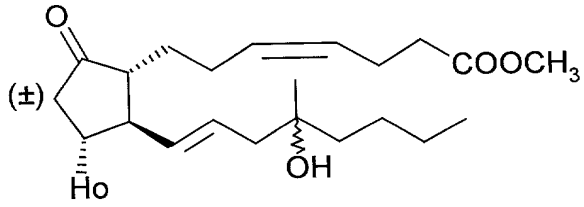
II) Gastric anti-secretory prostaglandin analogues suitable for the claimed therapies and formulations are for instance misoprostol, enprostil, enisoprost, rosaprostol, miraprostal and analogues with the following formulas



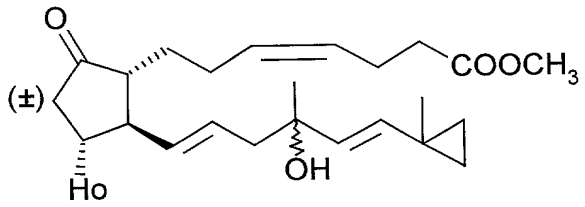
misoprostol

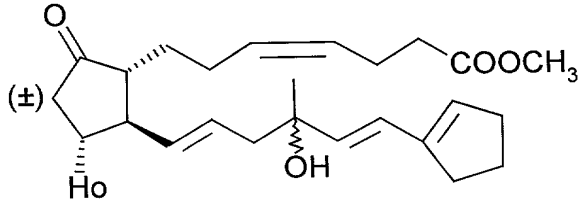


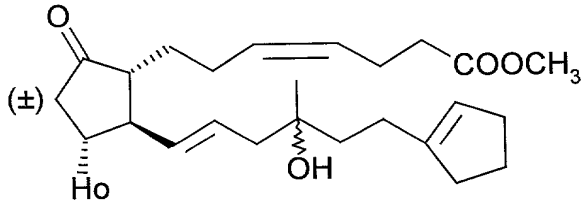
enprostil

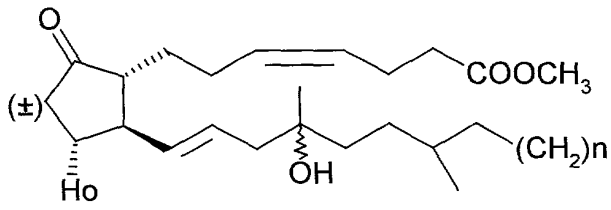


enisoprost









The above compounds may be used in the form of their single enantiomers.

III) Calcium channel blockers which optionally may be used in combination with a proton pump inhibitor and a gastric antisecretory prostaglandin analogue are for instance the following ones known under the generic names verapamil, felodipin, nifedipin and nisoldipine.

Use of the preparations

The dosage forms according to the present invention, are suitable for oral administration. The dose will depend on the nature and severity of the disease to be treated. The dose may also vary according to the age, body weight, and response of the individual patient. Children and patients with liver diseases as well as patients under long term treatment will generally benefit from doses that are somewhat lower than the average. In the treatment of other conditions higher doses than average will be used. The dosage forms may also be used in combinations with other dosage forms comprising for instance a calcium channel blocking agent, an NSAID, or other antiulcerative agents.

The dosage forms according to the invention are especially advantageous for patients experiencing gastrointestinal side-effects caused by gastric antisecretory prostaglandin analogues, when used alone. The new dosage forms are administered one to several times a day, preferably once or twice daily. The typical daily dose of the active substances varies and will depend on various factors such as the individual requirements of the patients, the

mode of administration and disease. In general each dosage form will comprise 1-200 mg of the H^+, K^+-ATPase inhibitor and 80 - 1 000 μg of the gastric antisecretory prostaglandin analogue(-s). Preferably, each dosage form will comprise 5-80 mg of the H^+, K^+-ATPase inhibitor and 100 - 800 μg of the gastric antisecretory prostaglandin analogue(-s), and more preferably 10-40 mg of the H^+, K^+-ATPase inhibitor and 150 - 600 μg of the gastric antisecretory prostaglandin analogue(-s), respectively. Especially preferred combinations comprise omeprazole and misoprotol in a range of 15: 1 to 400: 1, for instance 20 mg omeprazole together with 200 μg misoprostol, or 20 mg omeprazole and 400 μg misoprostol. In the latter one, misoprostol is preferably present in the form of an extended release formulation.

The optional calcium channel blocking agent may be present in an amount of 1 - 100 mg.

The multiple unit preparation, i.e. a capsule or a tableted dosage form, may also be suitable for dispersion in an aqueous liquid with slightly acidic pH-value. The dispension should be prepared just before being orally administered or fed through a naso-gastric tube.

The present invention is illustrated more by detail in the following non-limiting examples.

Examples

Example 1.

Two-layer tablet comprising misoprostol and omeprazole (magnesium salt).

Principle: one layer comprises 400 μg misoprostol in a hydrophilic matrix, and the other layer comprises 20 mg omeprazole (magnesium salt) in the form of enteric coated pellets mixed with tableting excipients.

Extended release granules comprising misoprostol were prepared according to this recipe;

Misoprostol	0.4 parts by weight
Ethanol 95% (w/v)	410 parts by weight
Hydroxypropyl methyl cellulose 50 cps	400 parts by weight
Sodium stearyl fumarate	4 parts by weight

The misoprostol was dissolved in half the amount of ethanol. This solution was poured on the HPMC powder during mixing. The rest of the ethanol was added to achieve a suitable consistence of the mass. The mass was dried under mild conditions, and the particle size of the dried granules was reduced until all granules passed a 0.8 mm sieve. 1% (w/w) of sodium stearyl fumarate was admixed.

Enteric coated pellets comprising omeprazole magnesium salt was prepared according to the following recipe;

Core material

Magnesium omeprazole	12.00 kg
Sugar spheres (non-pareil™)	12.00 kg
Hydroxypropyl methylcellulose	1.8 kg
Water purified	35.4 kg

Separating layer

Core material (acc. to above)	23.50 kg
Hydroxypropyl cellulose	2.35 kg
Talc	4.03 kg
Magnesium Stearate	0.34 kg
Water purified	48.00 kg

Enteric coating

Coated pellets (acc. to above)	29.00 kg
Methacrylic acid copolymer (30% suspension)	38.70 kg
Triethyl citrate	3.48 kg

Mono- and diglycerides (NF)	0.58 kg
Polysorbate 80	0.06 kg
Water purified	22.68 kg

Over-coating

Enteric coated pellets	44.7 kg
Hydroxypropyl methylcellulose	0.58 kg
Mg-Stearate	0.017 kg
Water purified	11.6 kg

Suspension layering was performed in a fluid bed apparatus. Magnesium omeprazole was sprayed onto non-pareil from a water suspension containing the dissolved binder and magnesium omeprazole.

The prepared core material was coated in a fluid bed apparatus with the separating layer material. The enteric coating was sprayed onto the coated pellets in a fluid bed apparatus. In the same type of apparatus the enteric coated pellets were coated with an over-coat. The over-coated pellets were classified by sieving.

Tableting excipient for mixing with enteric coated pellets was prepared by mixing the following ingredients to homogeneity;

Tableting excipient;

Microcrystalline cellulose special coarse grade PH 102		12.12 g
Microcrystalline cellulose PH 101		6.06 g
Polyvinyl pyrrolidone cross-linked		1.82 g
	Sum:	20.00 g

Tablets were compressed on a tablet machine equipped with 9x17 mm oval punches (giving elliptically shaped tablets), by pre-compressing 404 mg of the misoprostol-containing granules and then filling a mixture consisting of 100 mg omeprazole pellets (according to above) and 200 mg of the tableting excipient mix, and compressing. A two

layered tablet was obtained with an acid resistance of 91% (mean value of 4 tablets). The release of omeprazole at pH 6.8 from a tablet pre-exposed 2 h in 0.1 M HCl, spectrophotometric determination, was 89% within 30 min.

Example 2.

Enteric coated pellets comprising magnesium salt of S-omeprazole, layered with misoprostol.

Principle: enteric coated pellets comprising approx. 225 mg/g magnesium salt of S-omeprazole layered with an outer fast dissolving layer comprising approx. 3.6 mg/g misoprostol.

Enteric coated pellets comprising magnesium salt of S-omeprazole were prepared according to the following recipe;

Core material	
S-omeprazole Mg-salt	20.0 kg
Non-pareil™	25.0 kg
Hydroxypropyl methylcellulose (HPMC)	3.0 kg
Polysorbate 80	0.4 kg
Water purified	93.6 kg
Separating layer	
Core material (acc. to above)	50.0 kg
Hydroxypropyl cellulose	5.5 kg
Talc	20.5 kg
Magnesium Stearate	1.4 kg
Water purified	193.8 kg

Enteric coating

Coated pellets (acc. to above)	30.0	kg
Methacrylic acid copolymer (30% suspension)	30.0	kg
Triethyl citrate	0.9	kg
Mono- and diglycerides (NF)	0.5	kg
Polysorbate 80	0.05	kg
Water purified	12.9	kg

Suspension layering was performed in a fluid bed apparatus. S-omeprazole magnesium salt was sprayed onto non-pareil from a water suspension containing the dissolved binder. The prepared core material was coated in a fluid bed apparatus with the separating layer material. The enteric coating was sprayed onto the coated pellets in a fluid bed apparatus. The enteric coated pellets were classified by sieving.

The enteric coated pellets were further coated with a solution of HPMC and misoprostol in a fluid bed apparatus, using the following composition;

Enteric coated pellets (according to above)	100	g
Solution;		
EtOH 95% (w/v)	125	g
Misoprostol	0.46	g
Water, purified	125	g
Hydroxypropyl methyl cellulose (HPMC) 6 cps	5.3	g
Colloidal silica (Aerosil™)	0.5	g

First the misoprostol was dissolved in the ethanol and then the water was added. The HPMC was admixed and dissolved. Finally the Aerosil™ was dispersed in the solution. The obtained pellets were classified by sieving. The acid resistance of the prepared pellets was 99.6%. The prepared pellets may be mixed with tablet excipients and compressed into

a multiple unit tablet as described in Example 5, or filled into a capsule suitable for the desired dose.

Example 3.

Two-layer tablet with 400 μg misoprostol and 10 mg of felodipine comprised in a hydrophilic matrix as one layer, and the other layer comprising 20 mg omeprazole (magnesium salt) in the form of enteric coated pellets mixed with tableting excipients.

Extended release granules comprising misoprostol and felodine are prepared according to the following recipe;

	parts by weight
Misoprostol	0.4
Felodipine	10
Polyoxyl 40 hydrogenated castor oil (Cremophor RH 40)	10
Ethanol 95% (w/v)	400
Hydroxypropyl methyl cellulose 50 cps	400
Sodium stearyl fumarate	4

The misoprostol is dissolved in half the amount of ethanol. Another solution is made by dissolving 10 parts of the felodipine and 10 parts of the Cremophor RH 40 in 60 parts of ethanol. These solutions are poured on the HPMC powder during mixing. Additionally ethanol (approximately 140 parts) may be added to get satisfactory consistency of the mass. The mass is dried on a tray (under mild conditions). The particle size of the dried granules is reduced until all granules passed a 0.8 mm sieve. Thereafter 1% (w/w) of sodium stearyl fumarate is admixed.

Enteric coated pellets comprising omeprazole magnesium salt was prepared and mixed with tabletting excipients according to Example 1. Two-layer tablets containing

misoprostol 400 μg, felodipin 10 mg, and omeprazole 20 mg were prepared as described in Example 1.

The tablets are coated with a solution of HPMC and PEG having pigments dispersed therein, in a suitable coating apparatus, e.g. rotating drum coater, using the following composition;

Tablets (according to above)	724	parts by weight
Solution;		
Water purified	122	parts by weight
Hydroxypropyl methyl cellulose (HPMC) 6 cps	14	parts by weight
Polyethylene glycol (PEG) 6000	4	parts by weight
Titanium dioxide	2	parts by weight
Iron oxide yellow	2	parts by weight

The coating is continued until average tablet weight has increased with 14 - 20 mg.

Example 4.

Capsule formulation comprising pantoprazole and misoprostol pellets. (40 mg pantoprazole and 200 μg misoprostol).

Pantoprazole enteric coated pellets is prepared according to the following recipe;

Core material	
Pantoprazole	100 g
Non-pareil™	200 g
Hydroxypropylcellulose LF	25 g
Water purified	607 g

Separating layer

Core material (acc. to above)	200 g
Hydroxypropyl cellulose LF	20 g
Talc	34.3 g
Magnesium Stearate	2.9 g
Water purified	400 g

Enteric coating

Coated pellets (acc. to above)	200 g
Methacrylic acid copolymer, 30% suspension	333 g
Triethyl citrate	30 g
Mono- and diglycerides (NF)	5 g
Polysorbate 80	0.5 g
Water purified	281.5 g

Suspension layering is performed in a fluid bed apparatus. Pantoprazole is sprayed onto non-pareil from a water suspension containing the dissolved binder.
The prepared core material is coated in a fluid bed apparatus with the separating layer material. The enteric coating is sprayed onto the coated pellets in a fluid bed apparatus. The pellets are classified by sieving.

Misoprostol pellets are prepared by coating inert sugar spheres in a fluid bed according to the following recipe;

Sugar spheres (Non Pareil™)	100	g
Solution;		
EtOH 95% (w/v)	125	g
Misoprostol	0.46	g
Water, purified	125	g

Hydroxypropyl methyl cellulose (HPMC) 6 cps	5.34 g
Colloidal silica (Aerosil™)	0.50 g

First the misoprostol is dissolved in the ethanol and then the water is added. The HPMC is admixed and dissolved. Finally the Aerosil™ is dispersed in the solution. The obtained pellets are classified by sieving.

Capsule filling;

266 mg enteric coated pantoprazole pellets and pellets corresponding to 200 μg of misoprostol (i.e. approx. 55 mg) are filled into a No. 1 hard gelatin capsule.

Example 5.

Multiple unit tablet comprising lansoprazole and misoprostol pellets. (60 mg lansoprazole and 200 μg of misoprostol).

Lansoprazole pellets are prepared according to the following recipe;

Core material

Lansoprazole	370 g
Non-pareil™	400 g
Hydroxypropyl methylcellulose	76 g
Sodium laurylsulphate	2.8 g
Water purified	1360 g

Separating layer

Core material (acc. to above)	400 g
Hydroxypropyl cellulose	40 g
Talc	68.6 g
Magnesium Stearate	5.7 g
Water purified	800 g

Enteric coating	
Coated pellets (acc. to above)	400 g
Methacrylic acid copolymer 30% suspension	667 g
(containing dry materials	200 g)
Triethyl citrate	60 g
Mono- and diglycerides (NF)	10 g
Polysorbate 80	1 g
Water purified	420 g

Over-coating	
Enteric coated pellets	500 g
Hydroxypropyl methylcellulose	6.5 g
Mg-Stearate	0.2 g
Water purified	130 g

The enteric coated pellets comprising lansoprazole are prepared as described in Example 1, with lansoprazole replacing omeprazole.

Tablets	mg/tablet	
Pellets comprising lansoprazole (according to above)	approx.	285
Pellets comprising misoprostol (according to Ex . 4)	approx.	55
Microcrystalline cellulose PH 102		205
Microcrystalline cellulose PH 101		205
Polyvinyl pyrrolidone cross-linked		30
Sodium stearyl fumarate		4

First the microcrystalline celluloses and polyvinyl pyrrolidone are mixed to homogeneity. Then the lubricant sodium stearyl fumarate is admixed, and thereafter the lansoprazole comprising pellets and the misoprostol comprising pellets are added, and mixed until homogeneity.

Compression to tablets is done by compressing the mixture on a tablet machine equipped with 9x21 mm oval punches.

Example 6.

Two-layer tablet with 200 μg misoprostol in one layer, and the other layer comprises 10 mg S-omeprazole (magnesium salt) containing delayed pulsed release pellets mixed with tableting excipients.

Granules comprising misoprostol are prepared according to this recipe;

	parts by weight
Misoprostol	0.2
Ethanol 95% (w/v)	300
Water purified	110
Hydroxypropyl methyl cellulose 6 cps	50
Microcrystalline cellulose PH 101	350
Sodium stearyl fumarate	4

The misoprostol is dissolved in 200 parts of ethanol. This solution is poured on the HPMC and microcrystalline cellulose powders during mixing. Then a satisfactory amount of a mixture consisting of 100 parts of ethanol and 110 parts of water is admixed until satisfactory consistency of the mass is obtained. The mass is dried under mild conditions. The particle size of the dried granules is reduced until all granules pass a 0.8 mm sieve. Thereafter 1% (w/w) of sodium stearyl fumarate is admixed.

Preparation of delayed pulsed release pellets comprising magnesium salt of S-omeprazole (pellet strength approx. 44 mg/g).

Preparation of core material (spheres layered with drug).

A drug containing suspension is made according to the composition below;

S-omeprazole Mg-salt	100g
HPMC, 6cps	15 g
Polysorbate 80	2 g
Purified water	323 g

HPMC is dissolved in water during stirring with subsequent addition of Polysobate 80 and the drug. The suspension is sprayed onto 290 g of sugar spheres (Non-pareil) in a fluidized bed. The product weight is approx. 395 g.

Application of swelling layer

A (water free) suspension containing in water highly swellable substances is prepared according to the following composition;

Low-substituted hydroxypropylcellulose (L-HPC)	162 g
Hydroxypropylcellulose LF (HPC-LF)	74 g
Talc	354 g
EtOH (99.5%)	3100 g

HPC-LF is dissolved in ethanol during stirring, then the talc and the swelling agent L-HPC are added. The suspension is sprayed onto 175 g drug containing pellets from above in a Wurster equipped fluidized bed. The weight of the product is usually approx. 710 g.

Application of lag time controlling layer (semipermeable membrane).

A coating suspension is made according to the following formula;

Ethylcellulose, 10 cps	10 g
Talc	23 g
EtOH (99.5%)	1000 g

The ethylcellulose is dissolved in the ethanol during stirring, then the talc is added. Spraying of the suspension onto 150 g of pellets from above (0.61-0.71 mm obtained by sieving) is done in a Wurster equipped fluidized bed. The weight of the obtained pellets is usually approx. 175 g.

Application of enteric coating layer.

Pellets from above are enteric coated in a fluidized bed with a coating dispersion according to below;

Eudragit L30 D-55 (30 % w/w dispersion)	73.3g
Triethyl citrate (TEC)	6.6 g
Glycerol monostearate (GMS)	0.3 g
Polysorbate 80	0.03 g
Purified water	40.4 g

A homogenous coating dispersion is prepared by dispersing polysorbate 80 and glycerol monostearate in water. Tritehylcitrate is dissolved in the Eudragit dispersion and thereafter the two dispersions are mixed to obtain the coating dispersion.

The coating dispersion is applied onto 120 g pellets, using a Wurster equipped fluidized bed. The weight of the enteric coated pellets is usually approx. 140 g.

Preparation of tablets

Tableting excipient for mixing with enteric coated pellets is prepared by mixing the following ingredients to homogeneity;

Tableting excipient;	
Microcrystalline cellulose special coarse grade PH 102	12.12 g
Microcrystalline cellulose PH 101	6.06 g

Polyvinyl pyrrolidone cross-linked	1.82 g
Sum:	20.00 g

Compression to tablets is done on a tablet machine equipped with 9x21 mm oval punches (giving elliptically shaped tablets). The tablets are prepared by first pre-compressing 404 mg of the misoprostol-containing granules and then filling a mixture consisting of approx. 270 mg S-Omeprazole magnesium salt comprising pellets (according to above) and 270 mg of the tableting excipient mix.

Example 7.

Enteric coated tablet comprising 45 mg omeprazole (magnesium salt) in a hydrophilic matrix, having an outer fast dissolving coat upon the enteric coat, the outer coat comprises approx. 220 µg of misoprostol.

Extended release tablets comprising omeprazole Mg-salt (approx. 45 mg).

Granules for tablet cores are made according to the following composition (parts by weight);

Omeprazole Mg-salt	80
Hydroxypropyl methylcellulose 50 cps	300
Polyvinyl pyrrolidone (PVP) K-90	40
Ethanol 99.5% (w/v)	400

The PVP is dissolved in the alcohol. The other two ingredients are mixed and then moistened with the PVP-solution in a mixer. Thereafter the obtained mass is dried in a drying oven at 50°C. After milling in an oscillating mill through a 1.0 mm screen the obtained granules are mixed with tablet lubricant, according to the following composition (parts by weight);

Granules for tablet core	412
Sodium stearyl fumarate (Pruv®)	4

The ingredients are mixed whereafter the mixture is compressed to tablets (9 mm in diameter) having an average weight of 265 mg, on a tableting machine.

Separating layer coated tablets

Obtained tablets are coated first with a separating layer in e.g. a rotating drum coating apparatus, with a coating suspension of the following composition;

EtOH 99.5% (w/v)	85	parts by weight
Water purified	85	parts by weight
Hydroxypropyl methylcellulose 6 cps	10	parts by weight
Talc, micronized	2	parts by weight
Sum:	182	parts.

The coating of the tablets is continued until average tablet weight is approx 274 mg.

Enteric coated tablets

The tablets coated with a separating layer are coated with an enteric coating layer in the same equipment as for the preceeding coating step. The coating solution to be used has the following composition;

Hydroxypropyl methylcellulose phtalate (HP-55®)	19	parts by weight
Cetanol	1	parts by weight
Acetone	182	parts by weight
Ethanol (95% w/v)	78	parts by weight
Sum:	280	parts

Separating layer coated tablets are processed and the coating is continued until average tablet weight is 293 mg.

Enteric coated tablets coated with misoprostol layer

The enteric coated omeprazole Mg-salt tablets are coated with a solution of HPMC and misoprostol in e.g. a rotating drum coating apparatus, using the following composition;

Dispersion	
EtOH 95% (w/v)	125 parts by weight
Misoprostol	0.46 parts by weight
Water, purified	125 parts by weight
Hydroxypropyl methyl cellulose (HPMC) 6 cps	5.34 parts by weight
Colloidal silica (Aerosil RTM)	0.50 parts by weight

First the misoprostol is dissolved in the ethanol and then the water is added. The HPMC is admixed and dissolved. Finally the Aerosil™ is dispersed in the solution.

The coating is continued, until the average tablet weight is 296 mg.

Example 8.

Enteric coated tablet comprising 20 mg omeprazole (magnesium salt) in a hydrophilic matrix, having an outer hydrophilic matrix layer upon the enteric coat, the outer layer comprises 200 µg misoprostol.

Granules comprising omeprazole Mg-salt are prepared according to this recipe;

	mg/tablet
Omeprazole Mg-salt	22.5
Ethanol 95% (w/v)	90
Hydroxypropyl methyl cellulose (HPMC) 50 cps	50

Hydroxypropyl methyl cellulose (HPMC) 10000 cps	40
Polyvinyl pyrrolidone (PVP) K-90	6.5

The PVP is dissolved in the ethanol. This solution is poured on the mixed powders of the HPMC's and Omeprazole Mg-salt powder during continued mixing. The mass is dried on a tray at 50°C in a drying oven. After milling through a 0.8 mm screen the obtained granules are mixed with tablet lubricant according the following composition;

Granules	119 g
Sodium stearyl fumarate (Pruv®)	1 g

The mixing is performed in to homogeneity in a mixer, e.g. Kenwood. Then it is compressed to 6 mm in diameter tablets having an average weight of 120 mg on a tableting machine. The tablets are coated with a separating layer by using a solution of HPMC and coating, e.g. in a fluid bed coating apparatus or rotating drum coater, using the following composition;

EtOH 95% (w/v)	125	parts by weight
Water, purified	125	parts by weight
Hydroxypropyl methyl cellulose (HPMC) 6 cps	5.3	parts by weight

The HPMC is dissolved in the ethanol/water mixture. The coating is continued until average tablet weight has increased with 4 mg (i.e. if starting average weight is 120 mg, to 124 mg).

The obtained separating layer coated tablets are coated with an enteric coating layer in the same equipment as for the preceeding coating step. The coating solution has the following composition;

Hydroxypropyl methylcellulose phtalate (HP-55)	16 parts by weight

Cetanol		1 parts by weight
Acetyl tributyl citrate		1 part by weight
Acetone		153 parts by weight
Ethanol (95% w/v)		65 parts by weight
	Sum:	236 parts by weight

The tablets are coated until average tablet weight is 133 mg. The obtained enteric coated extended release omeprazole Mg salt tablets are dry coated in a suitable tableting machine with a granulate comprising HPMC and misoprostol prepared using the following composition;

Misoprostol	0.2 parts by weight
Ethanol 95% (w/v)	200 parts by weight
Hydroxypropyl methyl cellulose (HPMC) 50 cps	200 parts by weight

First the misoprostol is dissolved in the ethanol. Then the solution is poured on the HPMC powder during mixing. The mass is dried using mild conditions. Obtained dried granules are milled in an oscillating granulator equipped with a 1.0 mm screen.

For the manufacturing of each dry coated extended release tablet, one enteric coated omeprazole Mg-salt tablet and 200 mg of misoprostol comprising extended release granulate is used, and compressed with 10 mm diameter punches.

Example 9.

Capsule formulation comprising 20 mg pantoprazole and 400 μg of misoprostol, the latter comprised in a hydrophilic matrix plug.

Pantoprazole pellets are prepared as described in Example 5, with lansoprazole replacing pantoprazole.

Extended release plug comprising misoprostol is prepared by first making a granulation according to this recipe;

Misoprostol	0.4 parts by weight
Ethanol 95% (w/v)	110 parts by weight
Hydroxypropyl methyl cellulose 50 cps	118 parts by weight

The misoprostol is dissolved in 110 parts of ethanol. This solution is poured on the HPMC powder during mixing. The mass is dried under mild conditions. The particle size of the dried granules is reduced until all granules pass a 0.8 mm sieve. Thereafter the lubricant sodium stearyl fumarate is admixed, according to following recipe;

Granules according to above	118.4 parts by weight
Sodium stearyl fumarate	1.6 parts by weight
sum	120.0 parts by weight

The mixing is performed to homogeneity in a mixer. Then it is compressed to 6 mm in diameter plugs (tablets) having an average weight of 120 mg on a tableting machine.

Capsule filling;

One plug according to above and 95 mg pantoprazole comprising pellets are filled into a hard gelatine capsule of size no 1.

Example 10.

Enteric coated, layered tablet with dual pulsed release of S-omeprazole magnesium salt (2 x approx.15 mg), having an outer fast dissolving coat upon the enteric coat, the outer layer comprises 220 μg of misoprostol.

Granules

Granules for tablet cores are made according to the following composition;

	parts by weight
S-omeprazole Mg-salt	229
Microcrystalline cellulose, Avicel PH 101	151
Microcrystalline cellulose, Avicel PH 102 sp. Coarse grade	400
L-HPC	256
PVP-XL	302
Sodium laurylsulphate (SLS)	30
Water purified	1060

A granulating solution is prepared by dissolving the SLS in 460 parts of purified water. The powders above are mixed in a mixer after which the solution is added in an even stream. Thereafter approx. 600 parts of water is added during continued mixing, to give satisfactory consistence to the mass. The mass is dried in a drying oven at 50°C over night.

Preparation of tablet cores

After milling through a 1.0 mm screen the obtained granules are mixed with tablet lubricant, sodium chloride, and an additional amount of swellable substance, according the following composition;

	parts by weight
Granules for homogenous tablet core	400
Sodium chloride (passing 0.3 mm)	80
Sodium stearyl fumarate (Pruv®)	8
Polyvinyl pyrrolidone cross-linked (PVP-XL)	20

The mixing is performed in to homogeneity in a mixer, e.g. Kenwood. Then it is compressed to 6 mm in diameter tablets having an average weight of 126 mg on a tableting machine.

Application of lag time controlling layer (semipermeable membrane).

The tablets are coated in a Wurster equipped fluidized bed coating apparatus with a coating suspension following composition;

EtOH 99.5% (w/v)		291 parts by weight
Ethyl cellulose N-10		11 parts by weight
Talc, micronized		7 parts by weight
	Sum:	309 parts

The tablets are coated and the coating is continued until average tablet weight is 134 mg.

Application of drug containing layer

The obtained tablets are coated in the same equipment as above with a coating suspension of the following composition;

S-omeprazole Mg-salt		20 parts by weight
Hydroxypropyl methylcellulose 6 cps		13 parts by weight
Ethanol 99%		128 parts by weight
Water purified		128 parts by weight
	Sum:	289 parts.

The tablets are coated and the coating is continued until the average tablet weight is 162 mg.

Separating layer coated tablets

Obtained tablets are coated first with a separating layer, in e.g. a rotating drum coating apparatus, with a coating suspension of the following composition;

EtOH 99.5% (w/v)		85 parts by weight
Water purified		85 parts by weight
Hydroxypropyl methylcellulose 6 cps		10 parts by weight
Talc, micronized		2 parts by weight
	Sum:	182 parts.

The coating of the tablets is continued until average tablet weight is approx 166 mg.

Application of enteric coating layer

The obtained tablets are coated with an enteric coating layer in the same equipment as for the preceeding coating step. The coating solution has the following composition;

Hydroxypropyl methylcellulose phtalate (HP-55)		16 parts by weight
Cetanol		1 parts by weight
Acetone		153 parts by weight
Ethanol (95% w/v)		65 parts by weight
	Sum:	235 parts by weight

The tablets are coated and the coating is continued until average tablet weight is 177 mg.

The enteric coated dual pulsed release S-omeprazole Mg salt tablets are coated with a solution of HPMC and misoprostol e.g. in a fluid bed coating apparatus or rotating drum coater, using the following composition;

Tablets (according to above)	100	parts by weight

Solution;		
EtOH 95% (w/v)	125	parts by weight
Misoprostol	0.46	parts by weight
Water, purified	125	parts by weight
Hydroxypropyl methyl cellulose (HPMC) 6 cps	5.34	parts by weight
Colloidal silica (Aerosil™)	0.50	parts by weight

First the misoprostol is dissolved in the ethanol and then the water is added. The HPMC is admixed and dissolved. Finally the Aerosil™ is dispersed in the solution.

The coating is continued until average tablet weight has increased with 3 mg (i.e. if starting average weight is 177 mg, to 180 mg).

Example 11.

Two-layer tablet with pellets comprising 200 μg misoprostol and pellets comprising 20 mg omeprazole (magnesium salt) mixed with tableting excipients in one layer, and the other layer comprises 30 mg nifedipine in a hydrophilic matrix.

Extended release granules comprising nifedipine was prepared according to this recipe;

Nifedipine	30	g
Polyoxyl 40 hydrogenated castor oil	30	g
Ethanol 99.5% (w/v)	300	g
Ethyl cellulose N-10	20	g
Propyl gallate	0.06	g
Hydroxypropyl methyl cellulose 50 cps	175	g
Sodium aluminium silicate	75	g
Sodium stearyl fumarate	6	g

Nifedipine, polyoxyl 40 hydrogenated castor oil and propyl gallate are charged into the ethanol. This mixture is heated and stirred until a solution is formed, keeping the temperature of the mixture/solution at maximum 70°C. Then the ethyl cellulose is added and dissolved. The obtained solution is poored on a mixture of the HPMC and the sodium aluminium silicate powders during mixing. The mass is dried in an explosion safe drying cabinet, whereafter it is milled in an oscillating granulator having a screen with 1 mm openings. The obtained granules are mixed with the lubricant sodium stearyl fumarate for 2 minutes.

Enteric coated pellets comprising omeprazole magnesium salt were prepared as described in Example 1.

Misoprostol pellets are prepared by dissolving misprostol in ethanol and then mixing porous silica particles with this solution, according to the following recipe;

Misoprostol	0.16 parts by weight
Silica particles, porous, appr diameter 150 μm	53.14 parts by weight
Ethanol 95% (w/v)	42.5 parts by weight

The mass is dried under mild conditions. Obtained misoprostol pellets contain approx. 3.75 mg misprostol per gram.

Tableting excipients for mixing with omeprazole and misoprostol pellets are prepared by mixing the following ingredients to homogeneity;

Tableting excipient;

Microcrystalline cellulose special coarse grade PH 102	12.12 parts by weight
Microcrystalline cellulose PH 101	6.06 parts by weight
Polyvinyl pyrrolidone cross-linked	1.82 parts by weight

Sum:	20.00 parts by weight

Compression to tablets is done on a tablet machine equipped with 9x17 mm oval punches (giving elliptically shaped tablets). The tablets are prepared by first pre-compressing 336 mg of the nifedipine containing granules and then filling a mixture consisting of 100 mg omeprazol magnesium salt comprising pellets (according to above), 53 mg misoprostol containing pellets and 200 mg of the tableting excipient mix, giving a total tablet weight of 689 mg.

To protect the nifedipine in the tablets against photolytic degradation, the tablets are coated with a solution of HPMC and PEG having pigments dispersed therein, in a fluid bed coating apparatus or rotating drum coater, using the following composition;

Tablets (according to above)	336	parts by weight
Solution;		
Water purified	122	parts by weight
Hydroxypropyl methyl cellulose (HPMC) 6 cps	14	parts by weight
Polyethylene glycol (PEG) 6000	4	parts by weight
Titanium dioxide	2	parts by weight
Iron oxide yellow	2	parts by weight

The coating is continued until average tablet weight has increased with 15 - 20 mg.

Example 12.

Enteric coated pellets comprising approx. 225 mg/g S-omeprazole magnesium salt and misoprostol, approx. 3.5 mg/g pellet wherein the latter is positioned in an outer extended release layer.

Enteric coated pellets comprising S-omeprazole magnesium salt were prepared as described in Example 2.

The enteric coated pellets are coated with a solution of HPMC and misoprostol in a fluid bed apparatus, using the following composition;

Enteric coated pellets (according to above)	100 parts by weight
Solution;	
EtOH 95% (w/v)	300 parts by weight
Water, purified	50 parts by weight
Misoprostol	0.46 parts by weight
Hydroxypropyl methyl cellulose (HPMC) 50 cps	5.34 parts by weight
Colloidal silica (Aerosil™)	0.50 parts by weight

First the misoprostol is dissolved in the ethanol and then the water is added. Thereafter the HPMC is admixed and dissolved. Finally the Aerosil™ is dispersed in the solution. The obtained pellets are classified by sieving. The prepared pellets may be compressed into a multiple unit tablet as described in Example 5, or filled into a capsule suitable for the desired dose.

Claims

1. An oral pharmaceutical dosage form comprising a H^+, K^+-ATPase inhibitor and a gastric antisecretory prostaglandin analogue compound and optionally pharmaceutically acceptable excipients, wherein the dosage form is in the form of a fixed unit dosage form comprising at least these two pharmaceutically active components.

2. A dosage form according to claim 1, wherein the dosage form is a tablet formulation.

3. A dosage form according to claim 1, wherein the dosage form is a capsule formulation.

4. A dosage form according to any of claims 1-3, wherein the H^+, K^+-ATPase inhibitor compound is protected by an enteric coating layer, and optionally a separating layer is applied under the enteric coating separating the H^+, K^+-ATPase inhibitor from the enteric coating layer.

5. A dosage form according to claim 1, wherein the fixed dosage form in addition to the H^+, K^+-ATPase inhibitor and the gastric antisecretory prostaglandin analogue comprises a calcium channel blocking agent.

6. A dosage form according to any of claims 1-5, wherein the H^+, K^+-ATPase inhibitor is omeprazole, an alkaline salt thereof, one of its single enantiomer or an alkaline salt thereof.

7. A dosage form according to claim 6, wherein the H^+, K^+-ATPase inhibitor is omeprazole magnesium salt.

8. A dosage form according to claim 6, wherein the H^+, K^+-ATPase inhibitor is S-omeprazole magnesium salt.

9. A dosage form according to any of claims 1-5, wherein the H^+, K^+-ATPase inhibitor is lansoprazole, or one of its single enantiomers or a pharmaceutically acceptable salt thereof.

10. A dosage form according to any of claims 1-5, wherein the H^+, K^+-ATPase inhibitor is pantoprazole, or one of its single enantiomers or a pharmaceutically acceptable salt thereof.

11. A dosage form according to one of claims 1-10, wherein the gastric antisecretory prostaglandin analogue compound is misoprostol, enisoprost, enprostil or one of the single enantiomers thereof or a pharmaceutical acceptable salt thereof.

12. A dosage form according to any of claims 1-11, wherein the amount of the H^+, K^+-ATPase inhibitor is in the range of 1-200 mg and the amount of the gastric antisecretory prostaglandin analogue is in the range of 80 - 1 000 μg.

13. A dosage form according to any of claims 1-12, wherein the amount of the H^+, K^+-ATPase inhibitor is in the range of 5-80 mg and the amount of the gastric antisecretory prostaglandin analogue is in the range of 100-800 μg.

14. A tableted dosage form according to claim 2, wherein the tablet consists of two different layers, a first layer comprising the H^+, K^+-ATPase inhibitor and a second layer comprising the gastric antisecretory prostaglandin analogue.

15. A tableted dosage form according to claim 2, wherein the tablet formulation is a multiple unit tableted dosage form comprising

a) the H^+, K^+-ATPase inhibitor in the form of enteric coating layered pellets,

b) the gastric antisecretory prostaglandin analogue compound and optionally

c) pharmaceutically acceptable excipients

compressed together into a tablet, whereby the enteric coating layer covering the individual pellets has mechanical properties such that the tableting of the pellets together with the gastric antisecretory prostaglandin analogue and optionally pharmaceutically acceptable excipients does not significantly affect the acid resistance of the enteric coating layered pellets.

16. A tableted dosage form according to claim 15, wherein the enteric coating of the individual pellets comprises a plasticized enteric coating layer material.

17. A tableted dosage form according to claim 15, wherein the enteric coating layered pellets are further covered with an over-coating layer comprising a film forming polymer and pharmaceutically acceptable excipients.

18. A tableted dosage form according to any of claims 15-17, wherein the tablet is divisible.

19. A tableted dosage form according to claim 2, wherein at least one part of the tablet is in the form of an extended release formulation.

20. A tablet dosage form according to claim 19, wherein the part of the tablet giving extended release is a hydrophilic matrix.

21. A tablet dosage form according to claim 19, wherein the part of the tablet giving extended release is a hydrophobic matrix.

22. A tablet dosage form according to claim 2, wherein the tablet consists of two different layers, a first layer comprising the H^+, K^+-ATPase inhibitor in the form of enteric

coating layered pellets compressed with tablet excipients into a layer, and a second layer giving an extended release of the incorporated gastric antisecretory prostaglandin analogue.

23. A tableted dosage form according to claim 2, wherein the tablet comprises enteric coating layered pellets of the H^+, K^+-ATPase inhibitor layered with a further layer comprising the gastric antisecretory prostaglandin analogue, and the layered pellets are compressed with tablet excipients to a tablet.

24. A tableted dosage form according to claim 23, wherein the pellets before compression to a tablet is covered by a pigmented film coating layer, or the compressed tablet is covered by a pigmented tablet coat.

25. A tablet dosage form according to claim 2, wherein the tablet consists of two types of layered pellets, the first type consists of enteric coating layered pellets comprising the H^+, K^+-ATPase inhibitor and the second type consists of pellets comprising the gastric antisecretory prostaglandin analogue, all pellets are compressed together with tablet excipients to a tablet.

26. A tablet dosage form according to claim 22, wherein the tablet consists of enteric coating layered pellets comprising the H^+, K^+-ATPase inhibitor, and pellets comprising the gastric antisecretory prostaglandin analogue incorporated in a matrix giving an extended release of the prostaglandin analogue.

27. A dosage form according to claim 3, wherein the capsule comprises two types of layered pellets, the first type consists of enteric coating layered pellets comprising the H^+, K^+-ATPase inhibitor and the second type consists of pellets comprising the gastric antisecretory prostaglandin analogue, all pellets and optionally pharmaceutically acceptable excipients are filled in the capsule.

28. A process for the manufacture of a fixed dosage form comprising a H^+, K^+-ATPase inhibitor and one or more gastric antisecretory prostaglandin analogue(s) in a capsule, characterized in that the H^+, K^+-ATPase inhibitor is prepared in the form of enteric coating layered pellets, and the gastric antisecretory prostaglandin analogue is prepared in the form of pellets coating layered with an extended release film, the pellets are mixed, optionally with pharmaceutically acceptable excipients, and the mixture is filled in to capsules.

29. A process for the manufacture of a fixed dosage form comprising a H^+, K^+-ATPase inhibitor and one or more gastric antisecretory prostaglandin analogues in a multiple unit tableted dosage form, characterized in that the H^+, K^+-ATPase inhibitor is prepared in the form of enteric coating layered pellets and these pellets are mixed with pellets comprising the gastric antisecretory prostaglandin analogue, and optionally pharmaceutically acceptable tablets excipients, whereafter the mixture is compressed into multiple unit tablets without causing any significant change of the acid resistance of the enteric coating layered pellets.

30. A process for the manufacture of a fixed dosage form comprising a H^+, K^+-ATPase inhibitor and one or more gastric antisecretory prostaglandin analogues in a multiple unit tableted dosage form, characterized in that the H^+, K^+-ATPase inhibitor is prepared in the form of enteric coating layered pellets and the gastric antisecretory prostaglandin analogue is prepared in the form of coating layered pellets wherein the coating layer is an extended release layer, the pellets are mixed, optionally with pharmaceutically acceptable tablet excipients, and compressed into tablets without causing any significant change of the acid resistance of the enteric coating layered pellets.

31. A method for the treatment and profylaxis of gastrointestinal disorders by administering to a host in need thereof a therapeutic effective dosage form according to any of claims 1-27.

32. A method for avoiding gastrointestinal side-effects normally associated with gastric antisecretory prostaglandin analogue medicament treatment in mammals and man by administering to a host in need thereof a therapeutically effective dosage form according to any of claims 1-27.

33. Use of a dosage form according to any of claims 1-27 in the manufacture of a medicament for treatment or profylaxis of gastrointestinal diseases.

34. Use of a dosage form according to any of claims 1-27 in the manufacture of a medicament for avoiding gastrointestinal side-effects normally associated with gastric antisecretory prostaglandin analogue treatment.

35. A combination of a H^+, K^+-ATPase inhibitor, a gastric antisecretory prostaglandin analogue and a calcium channel blocking agent in the treatment of gastrointestinal diseases.

36. A blister pack comprising a H^+,K^+-ATPase inhibitor medicament and a gastric antisecretory prostaglandin analogue medicament.

37. A blister pack according to claim 36 comprising an additional medicament which is a calcium channel blocking agent.

ABSTRACT

This invention is related to new oral pharmaceutical dosage forms comprising a proton pump inhibitor, i.e. a H^+, K^+-ATPase inhibitor, a gastric antisecretory prostaglandin analogue compound, and optionally an additional drug such as a calcium channel blocking agent, especially for use in the treatment and prophylaxis of gastrointestinal disorders. More specifically the invention is related to new dosage forms comprising omeprazole and misoprostol. The invention is also related to a combination of the three categories of drugs, i.e. the H^+, K^+-ATPase inhibitor, the gastric antisecretory prostaglandin analogue, and the calcium channel blocking agent. Furthermore, the invention refers to a method for the manufacture of the described dosage forms and their use in medicine, as well as blister packs comprising these medicaments.

Docket Number (Optional) H 1927-1P US

DECLARATION FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled NEW PHARMACEUTICAL FORMULATION the specification of which is attached hereto unless the following box is checked:

☒ was filed on 10 December 1999 as United States Application Number or PCT International Application Number SE99/02315 and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56

I hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

			Priority Not Claimed
9804314-4 (Number)	Sweden (Country)	14 December 1998 (Day/Month/Year Filed)	☐
(Number)	(Country	(Day(Month/Year Filed)	☐

I hereby claim the benefit under 35 U.S.C. § 119(e) of any United States provisional application(s) listed below.

(Application Number)	(Filing Date)
(Application Number	(Filing Date)

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 112.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

(Application Number)	(Filing Date)	(Status -- patented, pending, abandoned)
(Application Number)	(Filing Date)	(Status -- patented, pending, abandoned)

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believe to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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(given name, family name) _____

Fifth inventor's signature _____ Date _____

Residence Address _____ Citizenship _____

Post Office Address _____

Additional inventors are being named on separately numbered sheets attached hereto.

Docket Number (Optional) H 1927-1P US

DECLARATION FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled NEW PHARMACEUTICAL FORMULATION the specification of which is attached hereto unless the following box is checked:

☒ was filed on 10 December 1999 as United States Application Number or PCT International Application Number SE99/02315 and was amended on _____ (if applicable).

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(Application Number	(Filing Date)

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 112.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

(Application Number)	(Filing Date)	(Status -- patented, pending, abandoned)
(Application Number)	(Filing Date)	(Status -- patented, pending, abandoned)

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believe to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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Additional inventors are being named on separately numbered sheets attached hereto.